REMARKS

Claims 99-103 and 107-128 are pending. Claims 95-98 and 104-106 have been canceled without prejudice to future prosecution. Applicants believe that the amendments and new claims add no new matter. New claim 128 finds support in cancelled claim 98 and in the specification at page 11, lines 15-39. No new matter is added with this claim.

Claims 95-127 stand rejected under 35 USC §112, first paragraph, as allegedly not enabled by the specification. Claims 109-112 stand rejected under 35 USC §112, second paragraph, as allegedly being indefinite. All the claims stand rejected under 35 USC §103 as being obvious over Lowe ('663). Claims 95, 96, 99, 100, 124, and 125 were rejected as obvious over Lowe in view of Koshitomo. Claims 124 and 125 stand rejected as obvious over Koshitomo. All of the rejections will be addressed in the order in which they were raised.

The Invention

The present invention is based in part on the discovery of oligosaccharide moieties recognized by selectin cell surface receptors, such as E-selectin and P-selectin. These receptors are involved, *inter alia,* in adhesion of various leukocytes to the vascular endothelium, an early step in many inflammatory responses. In particular, the application provides evidence that an oligosaccharide structure, referred to here as sialyl Lewis X (SLe^x, NeuAcα2,3Galβ1,4(Fucα1,3)GlcNAc——), is specifically recognized by activated endothelial cells expressing E-selectin (*see, e.g.*, Examples 1 and 4) as well as activated platelets expressing P-selectin (*see, e.g.*, Example 7). As explained in the specification at page 13, lines 3-10, a variant structure, SLe^a (formula II of claim 99), is also capable of binding selectin receptors. As discussed in detail below, the application provides further evidence that a number of other variants of the SLe^x structure are capable of blocking selectin-mediated adhesion (*see, e.g.*, Examples 8, 9, 16 and 17). Finally, evidence that such structures block cellular adhesion *in vivo* and are useful in inhibiting inflammatory responses is provided in Example 18 and 19.

Based on these data the applicants have identified a core trisaccharide structure (as shown at page 11, line 19 and in claim 99), that, when presented to selectin-expressing

cells, inhibits selectin-mediated binding. The application also provides teaching enabling one of skill to make and use pharmaceutical compositions comprising carbohydrate compounds which present the claimed core structure. These compositions are particularly useful inhibiting selectin-mediated intercellular adhesion and thereby treating a number of inflammatory conditions. The pending claims are directed to methods of using these compounds.

I. Rejections under 35 USC §112, First Paragraph

Claims 95-127 stand rejected under 35 USC §112, first paragraph, as allegedly not enabled by the specification. In particular, the Examiner alleges that, based on the present disclosure, one of skill would not expect compounds of the invention to bind more than one selectin receptor. In addition, the Examiner alleges that undue experimentation would be required to identify compounds within the scope of the claims.

A) The specification is enabling for compounds that bind more than one selectin.

The Examiner asserts that the specification provides "no enabling teaching of the manner in which one would choose which oligosaccharide compound to employ for selective binding of which selectin receptor" (Office Action page 7). This rejection is traversed in part and overcome in part by the above-amended claims.

In assessing enablement, a specification that has claims which correspond in scope to the teaching in the specification must be taken as enabling, unless there is reason to doubt the objective truth of the assertions of enablement. It is incumbent upon the Examiner to explain why the truth or accuracy of the statements in the application should be doubted. These assertions must be backed up with acceptable evidence or reasoning. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971).

The Office Action fails to present evidence or reasoning to support the assertion that one of ordinary skill would not expect a compound that binds one selectin receptor to bind another selectin receptor. Indeed, the specification clearly demonstrates that compounds of the invention bind more than one selectin. As noted above, the Example section provides extensive disclosure of compounds that bind both P- and E- selectins. (*See*, in particular, page 76, lines 36-38; page 80, lines 8-9). To expedite prosecution, however,

Applicants have amended claim 99, without prejudice to future prosecution of broader claims, to recite that the targeted selectin is a P-selectin or an E-selectin. In light of the clear support for compounds that bind both of these receptors, withdrawal of the rejection is respectfully requested.

B) The Examiner has not set forth a *prima facie* case for undue experimentation

Claims 95-101, 104, 108 and 120-127 were rejected because they allegedly allow for "essentially unlimited substitution" and that undue experimentation would be required to identify oligosaccharides within the scope of the claims. Of these claims, claims 99, 108 and 120-127 remain under examination. This rejection is respectfully traversed in part and overcome in part by the above amended claims.

It is well established that enablement is not precluded by the necessity of some experimentation, such as routine screening. As the Federal Circuit has stated, "the key word is 'undue', not 'experimentation'" in determining whether pending claims are enabled. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Indeed, that decision makes clear that a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

As noted by the Federal Circuit in *Wands*, determination of undue experimentation is not a single, simple determination, but a conclusion reached by weighing many factual considerations. In that case, the court specifically adopted the analysis used by the Board of Patent Appeals and Interferences for the determination of undue experimentation (*see*, *Wands* at 1404 and *Ex parte Forman* 230 USPQ 546 (BPAI 1986)). In particular, the factors (referred to herein as the Forman Factors) to be considered are as follows: (1) the quantity of experimentation necessary, (2) the amount of direction and guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the art, and (8) the breadth of the claims.

Little or no reasoning or evidence to support the rejection along the lines suggested by the court has been presented in the Office Action. The Examiner simply alleges that the claims allow for "unlimited substitution". The scope of the claims is, of

course only one of eight factors to be considered. As noted above, the present invention is based on the discovery of the carbohydrate ligand recognized by selectin receptors. This discovery provides important guidance to those of skill in the design of carbohydrate molecules which bind these receptors.

The application, moreover, provides further guidance in the form of extensive working examples of compounds within the scope of the claims which are capable of inhibiting selectin-mediated binding. For instance, applicants show that liposomes bearing a divalent SLe^x structure block binding of cells to activated endothelial cells, while lipids bearing related structures (*e.g.*, without sialic acid or fucose residues) do not (Example 4). Examples 7 and 16 show that hexasaccharides and pentasaccharides bearing the SLe^x structure are more potent inhibitors than the tetrasaccharide. Example 8 shows that a variety of glycolipids bearing carbohydrate moieties which terminate in N-glycollyl neuraminic acid (NeuGc) in place of N-acetyl neuraminic acid (NeuAc) are effective inhibitors. Example 12 shows that fucosylation of a bacterial polysaccharide (type 1a polysaccharide) converts the polysaccharide into a polyvalent SLe^x containing polysaccharide which inhibits selectin-mediated binding.

In Example 15 the preparation of a preferred pentasaccharide, identified as compound Z, are described. Examples 16 and 17 provide *in vitro* evidence of the inhibitory activity of this compound. Examples 18-20 demonstrate that this compound is effective in three different animal models of disease.

Also in Example 15, beginning at page 100, the preparation of a number of analogues of compound Z is described. Figure 12B shows the structure of these compounds as well as the inhibitory activity of each compound as determined in the assays described in Example 16.

The Examiner has provided no evidence or reasoning to show that, using the basic discovery disclosed here, the extensive evidence of activity provided in the application, and simple intercellular adhesion assays described there, one of skill (typically a PhD scientist) could not quickly and easily identify compounds capable of inhibiting selectin-mediated adhesion. In the absence of evidence or reasoning along the lines suggest by the court in *in re Wands*, the rejection is improper and should be withdrawn.

The Examiner also alleges that one of skill is "not taught by the specification how to make any conceivable oligosaccharide which might have desirable properties" (Office Action at page 7-12). Thus, the Examiner appears to be concerned that one of skill could not make oligosaccharides within the scope of the claims. The specification, however, provides disclosure of methods for preparing oligosaccharides of the invention from biological materials (page 17, line 8 to page 20, line 29). In addition, both chemical and enzymatic methods for preparing oligosaccharides of the invention are extensively described (*see, e.g.*, page 20, line 24 to page 30, line 14). Finally, Example 15 on pages 87-107 provides detailed description of the preparation of a number of preferred compounds of the invention. The Examiner has failed to show why one of skill could not synthesize oligosaccharides of the invention based on this detailed disclosure and general knowledge in the art.

Finally, the purposes of the patent system are undermined if applicants are limited to specific preferred embodiments when, as here, other operable embodiments may be discovered using the present disclosure and only routine experimentation. Limiting the protection to specific structures renders the invention easy to "design around". As the court has stated:

> To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials ... would not serve the constitutional purpose of promoting progress in the useful arts. *In re Goffe*, 191 USPQ 429, 431 (CCPA 1976).

In this case, a competitor guided by the instant application could begin with the SLe^x unit disclosed here, make modifications to the basic compound based on the modifications taught here, and verify that the desired activity is present using routine assays. Thus, any protection provided by narrow claims directed to the preferred embodiments could easily by passed. Applicants respectfully remind the Examiner that to provide effective incentives, claims must adequately protect inventors. *Goffe at* 431.

In conclusion, the Office Action fails to provide sufficient evidence and reasoning to support the rejection. Moreover, the present disclosure provides extensive teaching which would allow one of skill to make and use compounds which present the claimed core saccharide structure. The rejection is thus improper as applied to all claims and is particularly improper as applied to claims 114-123, which are specifically directed to

preferred embodiments of the present invention. Nonetheless, in light of the important advance provided by the present invention, adequate patent protection for this contribution to the art should be provided. Applicants therefore respectfully request that the rejection be withdrawn.

II. Rejections under 35 USC §112, Second Paragraph

Claims 109-112 were rejected as allegedly being indefinite. To improve clarity, the claims have been amended according to the Examiner's suggestions. In view of these amendments Applicants respectfully request that this rejection be withdrawn.

III. Rejections under 35 USC §103

All of the pending claims were rejected as being obvious over Lowe (U.S. Patent No. 5,324,663). In addition, claims 99, 100, 124, and 125 were rejected as obvious over Lowe in view of Koshitomo and claims 124 and 125 were rejected as obvious over Koshitomo. Applicants respectfully traverse these rejections.

A) Rejection over Lowe

The Lowe patent describes methods and compositions for the preparation of desired carbohydrate structures. In particular, it relates to isolating and using a variety of glycosyltransferases, such as fucosyltransferases, to modify oligosaccharides and polysaccharides (*see, e.g.*, Summary of the Invention, column 2). The patent discloses that the Lewis blood group antigens comprising a fucose residue serve as receptors for certain bacteria and that fucosylated glycoconjugates have been implicated in binding to selectins. As admitted by the Examiner, it does not disclose the particular structures of the claimed methods.

Applicants respectfully submit that the Examiner mistakenly reads the patent as teaching that the Lewis antigens are associated with selectin binding (*see, e.g.*, Office Action, page 10,lines 3-5). In the Office Action, the Examiner specifically refers to column 25, line 39 to column 26, line 10 of the Lowe patent. Although this section of the patent refers to Lewis antigens as receptors for bacteria, it teaches only that "glycoconjugates" comprising fucose residues are "implicated in modulating adhesive events between cells, like leukocyte-ELAM-1 interactions" (column 25, lines 53-60, *see, also*, column 34, lines 54-60).

Applicants were unable to identify any description of the role of Lewis antigens in selectin-mediated adhesion in the section of the patent cited in the Office Action[1].

As the Examiner is aware, to establish a *prima facie* case of obviousness, the Examiner must indicate where the prior art provides reason or motivation for one of skill to make the claimed composition or carry out the claimed method. The Examiner must also demonstrate that one of ordinary skill would have had a reasonable expectation of success in attempting to make the composition or carry out the method. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

Other than a general allegation that the invention is obvious over Lowe, nothing in Lowe has been identified that suggests the claimed methods. In particular, there is no showing as to why one of skill would make and use the particular structures in the claimed methods based on Lowe's disclosure that fucosylated glycoconjugates are implicated in intercellular adhesion. Moreover, there is no reasoning or evidence to show that, if the compounds were made, one of skill would have a reasonable expectation that they would be useful in inhibiting selectin-mediated intercellular adhesion. In the absence of such a showing a *prima facie* case of obviousness has not been established and the rejection should be withdrawn.

B) Rejection over Lowe in combination with Koshitomo

The rejection of claims 95, 96, 99, 100, 124 and 125 over Lowe in combination with Koshitomo is respectfully traversed. Koshitomo describes a glycolipid comprising eight or more sugar residues conjugated to ceramide for use an antirheumatic. The Examiner asserts that this reference teaches the core trisaccharide of claim 99. This reference, however, does not teach any moieties linked to the Gal residue on the end of the molecule. The invention of claim 99, in contrast, is directed to the use of compounds in

[1] The patent refers, however, to a co-pending application (USSN 07/603,018, filed October 25, 1990), which identifies the selectin ligand as the "sialyl Lewis x molecule" (*see*, column 23, lines 8-13). Should a patent issue from that application, it would not be prior art under 35 U.S.C. §102(e), as it has a filing date after the effective filing date of the present application (June 15, 1990). The Examiner has provided no evidence that this disclosure is present in Lowe's great-great grandparent application, filed in February of 1990.

which the Gal residue is further linked to a group, R^1. The Examiner has identified nothing in the cited reference which discloses or suggest such a modification of the compounds taught in Koshitomo.

In addition, the figure in the Koshitomo reference denotes each glycosidic linkage with a question mark. Applicants understand this notation as indicating that each of these linkages could be either in the α or β orientation. The reference therefore teaches a large number of compounds comprising a variety of combinations of linkages between each of the sugars. The Examiner has identified nothing in this reference which specifically teaches the particular combination of linkages of the compounds of the claimed methods.

In this rejection, the Examiner again alleges that Lowe teaches a connection between Lewis antigens and selectin receptors (*see*, page 11, last full sentence). As noted above, that part of Lowe's disclosure available as prior art teaches only that fucosylated glycoconjugates are implicated in selectin-mediated binding. Such a teaching is not sufficient to motivate one of skill to make the compounds of the claimed methods, or to modify the compounds of Koshitomo in the manner suggested in the Office Action.

In conclusion, neither of the cited references, alone or in combination, teach the particular structures of the claimed methods. The Examiner has failed to identify any teaching in either reference that would motivate one of skill to modify the compounds of these references in the manner suggested. In the absence of such a showing the rejection is improper and should be withdrawn.

C) Rejection over Koshitomo

The rejection of claims 124 and 125 over Koshitomo is obviated by the above amended claims. These claims are now dependent upon claim 99, which discloses specific carbohydrate compounds for use in the claimed methods. As explained above, the cited reference neither discloses nor suggests such compounds. Applicants respectfully request that the rejection be withdrawn.

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at

an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (415) 543-9600.

Respectfully submitted,

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